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MODE OF CLEAVAGE OF STEROID METHYL ETHERS WITH BF_3-ETHERATE*

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Steroid methyl ethers were found to open up with BF_3-etherate and acetic anhydride (1) to give the elimination product and epimeric acetates (2). But there was no clear idea about the mode of cleavage. We have now found that the mechanism of this cleavage can be represented as in Chart I. It means that cleavage from the steroid nucleus, assisted probably by an SN_2 attack of the acetate anion of the anhydride, gives the epimeric acetate at C_3 as shown in (I) and (II), whereas similar cleavage from the methoxy methyl side, followed by attack on the complex by the acetylium cation (3), gives rise to the acetate with retention of configuration as shown in (IV) and (V). [In the cleavage from the nucleus (II), it is quite possible that some acetate with retention of configuration is also produced by an SN_1 process as has been found in the solvolysis of 3β- and 3α-cholestanyl chlorides (4)].

In other words, the anionic species of the reagent

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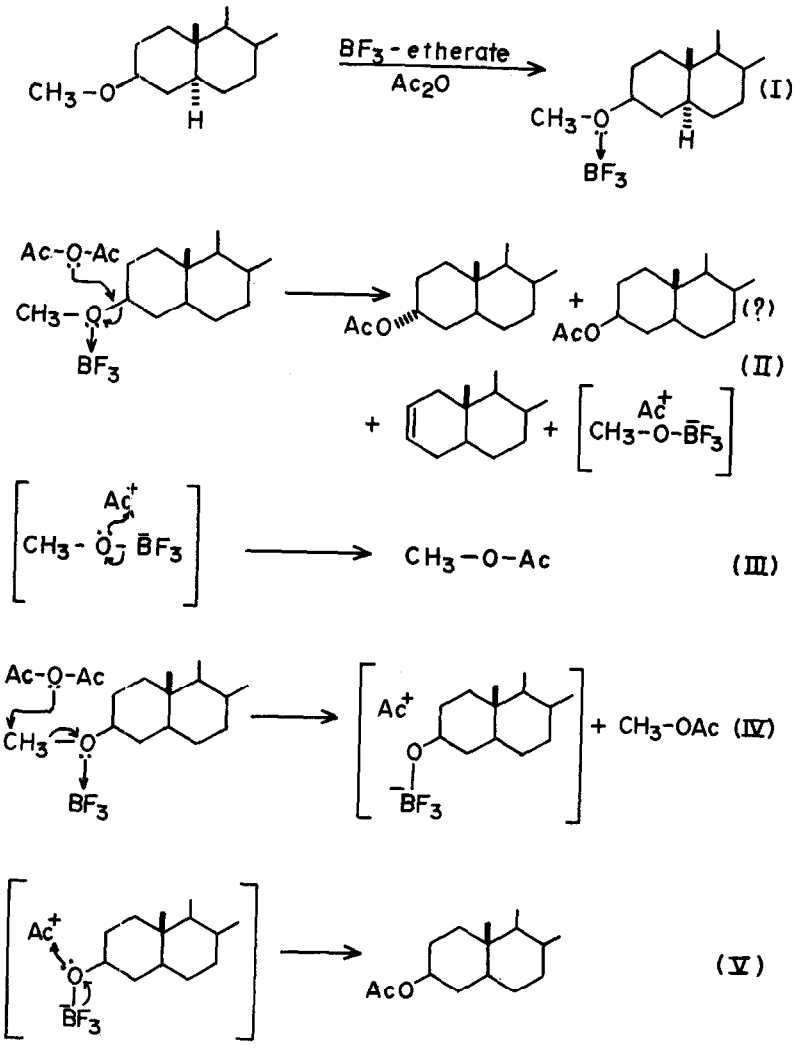
FIG. 1



(here AcO^-) gives rise to substitution with epimerization, and the cationic species (here Ac^+) gives rise to a derivative with retention of configuration. As the products from both types of cleavages are the epimeric steroid acetates and methyl acetate in the present case, the evidence from this product composition was not very clear. We therefore conducted the reaction with a reagent which can give different products by combination with its anionic and cationic species.

Thus cholestanyl methyl ether, on treatment with acetyl chloride and BF_3-etherate gave, besides Δ^2-cholestene (38%), a mixture of 3α and 3β-cholestanyl chlorides (12.5%), and cholestane-3β-ol-acetate (21%), in complete agreement with the above mechanism. The compounds were first identified from the mixture by IR and PMR spectra, and later estimated after hydrolysis and chromatography, the acetate being characterised as cholestane-3β-ol.

Similarly cholestane-3α-ol methyl ether, on treatment with the same reagents gave, besides Δ^2-cholestene (60%), a mixture of cholestane-3α- and 3β-chlorides (4%), and cholestane-3α-ol acetate (7%) as expected. As before, the acetate was characterised as cholestane-3α-ol. Addition of anhydrous lithium iodide to cholestanyl methyl ether along with the reagents improved the yield of cholestanyl acetate to 28%. This reaction thus also provides a method to regenerate the starting alcohol uncontaminated

with its epimer.

It was found before (2) that cholesteryl methyl ether with BF_3-etherate and acetic anhydride gives only one product viz. cholesteryl acetate (93%). This can be explained by the formation of the acetate with retention of configuration as in (IV, V), together with substitution from the steroid nucleus as in (II), but in the latter case, the stabilisation of the carbonium ion at C_3 from the Δ^5-bond, giving only the more stable equatorial acetate. As both products were the same, there was no evidence before for both types of cleavages, and no idea of the relative amounts of each. Now, conducting the reaction with acid chlorides and BF_3-etherate, these objectives could be achieved.

Six different acid chlorides were used for the reaction, and the relative percentages of the chloride in the mixture of the steroid chloride and ester were determined by comparing the intensities of the C — Cl stretching frequency in the IR spectra (5). The amount of the ester was found by difference. In the case of the acetyl chloride, the reaction product was hydrolysed, and the cholesteryl chloride and cholesterol were separated by chromatography and estimated. The difference from the values obtained spectroscopically was found to be less than 3%. The results obtained with the acid chlorides are tabulated in Table I.

TABLE I

	Acid chloride used.	Percentage of Cholesteryl chloride formed	Ester formed
1	Acetyl	63.5	22.3
2	Propionyl	68.2	20.5
3	Butyryl	62.7	23.2
4	Isobutyryl	66.5	26
5	Isovaleroyl	63.7	21.3
6	Benzoyl	61.3	22.7

It is interesting that in everyone of the cases studied with acid chlorides, substantial amount of cleavage is found to take place from the methoxy methyl side, to produce the esters concerned. The simple aliphatic acid chlorides give almost the same pattern of cleavage. In the case of cholestanyl methyl ether, the products obtained from the nucleus viz., Δ^2-cholestene and cholestane-3α and 3β-chlorides, together come to a yield of 50.5%, whereas in the case of cholesteryl methyl ether, the corresponding cleavage product viz. cholesteryl chloride comes to over 60% in the six cases studied. In the latter case, besides the fact that there is no elimination product, there is an increased yield of the cleavage product from the nucleus. This can be taken as a measure of the stability given to the carbonium ion at C_3 by the

^{5}-bond under the reaction conditions (6). The product analysis of the saturated equatorial ether viz. cholestanyl methyl ether shows that two-thirds of the total products come by cleavage from the nucleus and one-third by cleavage from the other side, and in the homoallylic equatorial ether viz. cholesteryl methyl ether, the proportion is three-fourths and one-fourth respectively, as is to be expected.

By using an equimolar mixture of two different acid chlorides instead of one in this reaction, relative activities of the two acid chlorides can be determined by finding the proportion of the two different esters produced after the reaction. This reaction can also be used to find the mode of cleavage of mixed anhydrides by using the anhydride in the reaction and finding the configuration and relative amounts of the two esters produced. These could now conveniently be done by PMR spectroscopy.

REFERENCES

1 R.D.Youssefyeh and M.Mazur, Tetrahedron Letters No.26, p.1287 (1962).

2 C.R.Narayanan and K.N.Iyer, Tetrahedron Letters No.14, 759 (1964); full paper, J. Org. Chem. 30 (in press).

3 H.A.E.Mackenzie and E.R.S.Winter, Trans. Faraday Soc. 44, 161 (1948).

4 C.W.Shoppee, J. Chem. Soc. 1138 (1946).

5 D.H.R.Barton, J.E.Page and C.W.Shoppee, J. Chem. Soc. 331 (1956).

6 M. Simonetta and S. Winstein, J. Am. Chem. Soc. 76, 18 (1954).